b) combining a plurality of said amino acid residues to generate a secondary library of secondary sequences; wherein at least one of said secondary sequences is different from said primary sequences.

27. (New) A method according to claim 26 further comprising synthesizing a plurality of said secondary sequences.

28. (New) A method according to claim 27 wherein said synthesizing is done by multiple PCR with pooled oligonucleotides.

29. (New) A method according to 28 wherein said pooled oligonucleotides are added in equimolar amounts.

30. (New) A method according to claim 28 wherein said pooled oligonucleotides are added in amounts that correspond to the frequency of the mutation

REMARKS

Applicants thank Examiner Wessendorf for the opportunity to meet and for taking time to discuss this case on March 10, 2003. Claims 12-26 are pending in the present application. Claim 25 has been canceled. Claim 26 has been newly added.

In the Specification:

- Embedded Hyperlinks

All references to the hyperlinks and/or other forms of browser-executable code have been deleted from the Specification.

- Incorporation by Reference:

Applicants respectfully submit that referenced incorporated material is nonessential subject matter referred to for purposes of indicating the background of the invention or illustrating the state of the art.

Therefore, incorporation by reference is proper. In light of the foregoing, the Applicants request reconsideration and withdrawal of the objection to the Specification.

The current status of USSN: 09/127,926 has been added to recite "USSN: 09/127,926, now US Patent No. 6,269,312, issued July 31, 2001," as requested by the Examiner.

In the Claims:

Claim 12 has been amended to recite "secondary sequences," instead of "secondary variants" to clarify the claim language. Additionally, the claim has been amended to recite "primary sequences," instead of "primary variants" to clarify the claim language. A force field calculation may be used to generate a secondary library directly no primary library need be generated. See Spec at page 15, lines 10-14. Support for amendment to the claim may be found in the Specification at page 2, lines 11-15, and page 27, lines 5-9.

Claim 13 has been amended to recite "Self-Consistent Mean Field (SCMF)," instead of merely "SCMF." The acronym is well known in the art. Applicants submit that no new matter has been added by the recitation of the full name of this force field calculation. Addition of the spelled out force field calculation may be found on page 14, lines 23-28 of the Specification. A copy of the publication by Koehl et al., "Application of a Self-consistent Mean Field Theory to Predict Protein Side-chains Conformation and Estimate their Conformational Entropy," J. Mol. Biol. 239:249-75 (1994) has been attached hereto as Exhibit A for the Examiner's convenience. No new matter has been added by spelling out the acronym. See Specification at page 14, lines 23-28.

Claim 16 has been amended to recite "secondary sequences," instead of "secondary variants" to clarify the claim language. Additionally, the claim has been amended to recite "primary sequences," instead of "primary variants" to clarify the claim language. Support for these amendments may be found in the Specification at page 2, lines 11-15, and page 27, lines 5-9. The term "protein variants" is described in the Specification at page 8, lines 13-15 and page 9, lines 1-7. Applicants respectfully submit the terms "primary," "secondary," and "tertiary" as used in the claims are well known in the art within the context that each term in used in the claims. For example, "primary sequences" as opposed to "secondary library" and "tertiary library." See Specification at page 34, line 20-22, and original Claims 16 and 17. The term "plurality" is defined in the Specification beginning on page 26, line 27, ending at page 27, line 4. Additionally, the term "computational ranking" has been modified to recite "computationally ranking," making the term grammatically correct in the context of the claim.

Claim 26 has been newly added. An SCMF calculation may be used to produce a primary library of sequences or used directly to generate a secondary library. Support for the addition of Claim 26 may be found in the specification at beginning at page 14, line 23, ending on page 15, line 14.

Claims 27-30 are also newly added. Support for the addition of Claims 27-30 may be found in original Claims 21-24 respectively. No new matter has been added by this amendment.

Rejection under 35 USC §112, first paragraph

Claims 12-25 are rejected under 35 USC §112, first paragraph because the specification while enabling for the enzymes protein design using specific program design, does not reasonably provide enablement for any type of secondary library of scaffold protein variants or sequences.

The Applicants respectfully disagree for the following reasons. §112 does not require such extensive disclosure. A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ81, 94 (Fed.Cir. 1986), cert.denied, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ481, 489 (Fed. Cir. 1984).

Furthermore, "[a]ll that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further, the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. Se, e.g., *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)." (See MPEP §2164.08)

The Applicants respectfully points the Examiner's attention to page 8, lines 13-21 of the Specification as filed, where there is a discussion of secondary library of scaffold protein or variant sequences.

The enablement requirement refers to the requirement of 35 U.S.C. 112, first paragraph that the specification describe how to make and how to use the invention. The invention that one skilled in the art must be enabled to make and use is that defined by the claim(s) of the particular application or patent.

With respect to the scope of the enabling disclosure not commensurate with the scope provided in the Specification, there is disclosure of using a force field or alignment program as embodiments of the invention. See Specification at page 14, beginning at line 23 through page 15, ending on line 14 and page 12, beginning at line 29, through page 13, ending at line 28. The use of a probability distribution table is merely an embodiment of the present invention see page 28, lines 19-23. Additionally, there is no restriction to generating a probability distribution table using a force field calculation as suggested by the Examiner. See Specification at page 29, lines 5-36.

Applicants respectfully point to *In re Goffe*, 191 USPQ429 (CCPA 1976), where the court stated:

> "For all practical purposes, the Board would limit Appellant to claims involving the specific materials disclosed in the examples, so that a competitor seeking to avoid infringing the claims would merely have to follow the disclosure in the subsequently issued patent to find a substitute. However, to provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found to work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional propose of promoting progress in the useful arts."

Additionally, in *In re Angstadt*, 190 USPQ 214, 218 (CCPA 1976), the court further stated:

> "Appellants have apparently not disclosed every catalyst which will work; they have apparently not disclosed every catalyst which will not work. The question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with every species covered by a claim. To require such a complete disclosure would apparently necessitate a patent application or applications with "thousands" of examples or the disclosure of "thousands" of catalysts along with information as to whether each exhibits catalytic behavior resulting in the production of hydroperoxides. More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed."

Therefore, in conclusion, Applicants submit that the Specification taken in conjunction with the state of the art at the time the invention was filed fully enables a person skilled in the art to practice the method of the invention without undue experimentation. The claims have been amended to clarify the claim language. Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection under 35 USC §112, second paragraph

Claims 12-25 are rejected under 35 USC §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter, which the applicant regards as the invention.

Claims 12 and 16 are rejected as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. (MPEP 2172.01) The Examiner states that the following steps

have been omitted: 1) how the mere use of a force field calculation produces a probability distribution table of amino acid residues in a plurality of variant positions and 2) how the combining of the probability distribution of amino acids that results in a secondary sequence.

Applicants respectfully point out that force field calculations may be used to create a probability distribution table based on the results of the calculations. See Specification at page 28, lines 19-23. A probability distribution table is merely a means for tracking the frequency at which a particular residue appears at the variable positions. See Specification at page 29, lines 5-35. Specification at page 14, lines 23-35; page 15, lines 1-14; page 22, lines 1-22; and page 29, lines 5-36. As is well known in the art, the results of a force field calculation or other computational method may be analyzed in a probability distribution table. The specification contains several references for this method. See Specification at page 2, lines 16-22; page 13, lines 6-20; page 15, lines 1-14; page 24, lines 3-8; page 28, lines 19-23. Combining the amino acids at various positions that appear in the distribution table results in a secondary sequence. See Specification at page 2, lines 16-22.

Claim 13 has been amended to recite "Self-Consistent Mean Field (SCMF)" to remove the Office Action's objection that the acronym is ambiguous. A copy of the publication by Koehl has been attached hereto for the Examiner's convenience.

Claims 14, 15, 17, and 18 have been rejected as not further limiting the base claim. Applicants disagree that Claims 14, 15, 17, and 18 broaden the respective base claims because they recite a trademarked name for a defined computer program. See Specification page 2, lines 4-6 and page 15, lines 15-29. MPEP 608.01(v) states:

> "The use of a trademark does not render the claim indefinite, uncertain or arbitrary because the trademarks meaning is established by an accompanying definition which is sufficiently precise and definite to be made a part of a claim."

Claim 16 has been rejected as to the use of "alignment program" as being indefinite. Applicants respectfully disagree because alignment programs are well known in the art and are disclosed in the Specification. See Specification at page 7, lines 24-26; page 12, lines 12-17 and lines 29-30; and page 13, lines 1-28. Claim 16 has been amended to recite "computationally ranking," instead of "computational ranking" to correct the grammatical error. Support for the amended language may be found in the Specification at page 8, lines 8-12.

As stated in the MPEP §2173.05(a):

> The meaning of every term used in a claim should be apparent from the prior art or from the specification and drawings at the time the application is filed. Applicants need not confine themselves to the terminology used in the prior art, but are required to make clear and precise the terms that are used to define the invention whereby the metes and bounds of the claimed invention can be ascertained. During patent examination, the pending claims must be given the broadest reasonable interpretation consistent with the specification. *In re Morris*, 127 F.3d 1048, 1054, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997); *In re Prater*, 415 F.2d 1393, 162 USPQ 541 (CCPA 1969). See also MPEP § 2111 - § 2111.01. When the specification states the meaning that a term in the claim is intended to have, the claim is examined using that meaning, in order to achieve a complete exploration of the applicant's invention and its relation to the prior art. *In re Zletz*, 893 F.2d 319, 13 USPQ2d 1320 (Fed. Cir. 1989).

In reviewing a claim for compliance with 35 U.S.C. §112, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required (See MPEP §2173.02). If the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is precise as the subject matter permits, the statute demands no more.

Claims 19 and 20 have been rejected as being indefinite for the difference between sequence and structural alignment programs because there is an alleged absence of positive showing in the Specification. As discussed above, if the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is precise as the subject matter permits, the statute demands no more.

Applicants respectfully directs the Examiner's attention to page 7, lines 22-30;page 12, lines 12-17; page 12 beginning on line 29, ending on page 13 at line 5; and page 13, lines 21-28 of the Specification for discussion of the difference between alignment programs.

Claims 21-25 have been rejected as not further limiting the base claims from which they depend. Applicants respectfully disagree because Claims 21-24 are directed at synthesizing the secondary sequences of Claims 12 or 16. Claim 25 has been canceled, therefore the rejection with respect to this claim is made moot. Applicants have amended claim 24 to properly depend from claim 21. Applicants submit that the dependency modification makes Claim 24 definite.

Further, the term "equimolar" is a term of art and would be understood by one skilled in the art to mean equal. Specification at page 31, lines 12-14. Applicants respectfully submit the Examiner has

taken the term "corresponds" out of context. The term is used in connection with the frequency of mutation as described in the Specification. This concept is well known in the art. See Specification at page 28, lines 13-34; page 29, lines 1-4; page 30, lines 7-18; and page 31, lines 15-18.

The Office Action concludes that Claims 21-23 relate to synthesis of oligonucleotides, not proteins. Applicants respectfully submit that Claims 21-23 are directed to synthesizing the protein sequences of the preceding claims. See Specification at page 30 lines 19-33 page 31, lines 8-17, and page 33, line 1 through page 34, line 28. Claim 24 has been amended to correct the dependency of the claim to make the language more clear. Support for the changes may be found in the Specification at page 31, lines 15-17.

In light of the foregoing arguments, Applicants respectfully request the reconsideration and withdrawal of the rejection of Claims 12-25.

DOUBLE PATENTING

Claims 16-20 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over:

1. Claims 1 and 22 of U.S. Patent No. 6,269,312
2. Claims 1-8 of U.S. Patent No. 6,403,312

- U.S. Patent No. 6,269,312:

With respect to U.S. Patent No. 6,269,312, the present application is currently assigned to a different party from the assignees of this patent. A Terminal Disclaimer would therefore be inappropriate in this case. Applicants thus choose instead to respectfully traverse the rejection, and provide below remarks in support of the traversal.

As a preliminary matter, Applicants submit, that in determining whether a non-statutory basis exists for a double patenting rejection, the question to ask is not whether the claims of the instant application are embraced or encompassed by the claims of another patent, but rather whether any claim in the instant application defines an invention that is merely an obvious variation of an invention claimed in another application or patent. See M.P.E.P. §804.

An obviousness-type double patenting rejection is analogous to the obviousness rejection based on 35 U.S.C. §103, except that only the claims in the cited patents or applications are considered prior art. See M.P.E.P. §804. Therefore, the analysis employed in an obviousness-type double patenting rejection parallels the analysis of a 35 U.S.C. §103 obviousness determination, and a *prima facie* case

of obviousness must be established. See *In re Braat*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991).

Claims 1 and 22 of Patent No. 6,269,312 are directed to a method executed by a computer for automated protein design. Claim 22 further requires the use of at least one scoring function.

As the Examiner is aware, to make a *prima facie* case of obviousness, all claim limitations must be taught or suggested in prior art. See M.P.E.P. §2143.03.

By way of summary, the present invention is directed to the use of a variety of computational methods, to generate computationally pre-screened secondary libraries of proteins, and methods of making and methods and compositions utilizing the libraries. Specification at page 1, lines 3-5, and page 7, lines 22-30.

Claim 16, uses an alignment program to generate a probability distribution table of amino acid residues in a plurality of variant positions combining a plurality of said amino acid residues to generate a secondary library of secondary sequences, where at least one of the secondary sequences is different from the primary sequence(s) and computationally ranking the secondary library. None of the claims in the above-cited patent explicitly teach or suggest a method of generating secondary libraries using alignment programs.

Claims 17, 19-20 are dependent claims of claim 16. Claim 18 is dependent claim of 17.

While the claims in the above-cited patent are all related to automated protein design, they are silent about generation of secondary protein libraries and the use of a probability distribution table. The Examiner references the cited patent as disclosing an alignment program at column 3, line 51. However, only the claims of the cited reference may be used as prior art against the present application. Since not every limitation in the present claims are taught or suggested, a *prima facie* case of obviousness for double patenting rejection has not been established. Further, the alignment used in the context of col. 3, line 51 is a visual lining up of sequences after the computational steps have been completed. An alignment program as defined in the instant invention is not disclosed or taught in US 6,269,312.

Applicants accordingly submit that claims 16-20 of the present application are not obvious variations of the claims in the cited patents and request the double-patenting rejection be withdrawn.

- U.S. Patent No. 6,403,312:

Claims 1-8 of Patent No. 6,403,312 are directed to methods for generating a secondary library of scaffold protein variants. Claims 1-8 of U.S. Patent No. 6,403,312 are directed to a method for generating a secondary library of scaffold protein variants, providing a primary library, including providing a computationally rank-ordered list of scaffold protein primary variant sequences comprising primary variant positions.

In contrast, Claim 16 of the present invention is directed to the use of a variety of computational methods, to generate computationally pre-screened secondary libraries of proteins, using an alignment program. Specification at page 1, lines 3-5, page, page 12, lines 12-17, page 12, beginning at line 29, ending on page 13, line 20, page 13, beginning at line 21, ending on page 14, line 5.

Claims 17, 19-20 are dependent claims of claim 16. Claim 18 is dependent claim of 17. Claims 16-20 in the present application contain the limitation of generating protein libraries and using an alignment program.

As the Examiner is aware, to make a *prima facie* case of obviousness, all claim limitations must be taught or suggested in prior art. See M.P.E.P. §2143.03.

As discussed above, the inquiry is whether any claim in the instant application defines an invention that is merely an obvious variation of an invention claimed in another application or patent.

While the claims in the above-cited patent are all related to automated protein design, and generating secondary libraries of scaffold protein variants, they are silent about generation of protein libraries, from a probability distribution table of amino acid residues in a plurality of variant positions using an alignment program. Furthermore, with regard to claims 16-20 of the present application, none of the claims in the above-cited applications explicitly teach or suggest a method of using an alignment program. Since not every limitation in the present claims are taught or suggested, a *prima facie* case of obviousness for double patenting rejection has not been established.

Applicants accordingly submit that claims 16-20 of the present application are not obvious variations of the claims in the cited patents and request the double-patenting rejection be withdrawn.

Claim Rejections – 35 USC §102

Claims 12-15 have been rejected under §102(b) as being anticipated by Dahiyat et al. (Protein Science). The Office Action asserts that "Dahiyat discloses at page 896 a method by which protein variants are made by protein design automation (PDA) to create a secondary library of protein variant

sequences (rotamers)." Furthermore, "that the side chains are described by rotamers and an atomistic force field is used to score rotamer arrangements." Additionally, "[t]he conformationally site (rotamers) was varied that result in a protein having a secondary sequences different from the primary sequence from which the secondary sequences (containing a library of rotamers) are obtained." Finally, the Office Action concludes that "the specific process steps of Dahiyat using force field to score rotamer arrangement (probability distribution table of residues, as claimed) fully meet the broad claimed process step."

Claims 16-20 have been rejected under §102(b) as being anticipated by Dahiyat et al. (Science) because a method of generating a secondary protein variant comprising designing by protein design automation the secondary structure (rotamers) of beta beta alpha motif of the zinc finger DNA binding module is described and an alignment of the modified structure of the zif268 is made using a BLAST program.

Claims 1-20 have been rejected under §102(b) as being anticipated by Mayo et al. WO 98/47089, which corresponds to US Pat. No. 6,188,965, issued February 13, 2001. The Office Action states Mayo discloses the same method steps as each of the Dahiyat references for the use of force field calculations in generating secondary structures for protein variants (rotamers).

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989)."

As a preliminary matter, Applicants respectfully submit the Examiner has mischaracterized the term rotamers. As used in the present invention, rotamers are a representation of each amino acid, by a discrete set of all allowed conformers of each side chain. Specification at page 15, line 25-29.

Furthermore, the present invention may be distinguished from all the cited references because there is no suggestion or teaching of generating a secondary library from secondary sequences, differing from the primary sequence(s). Therefore, the claims of the present invention are not anticipated by the cited references because each and every element as set forth in the claim is not found, either expressly or inherently described, in a single prior art reference. In light of the foregoing, Applicants respectfully request reconsideration and withdrawal of the claim rejections.

Claim Rejections – 35 USC §103

Claims 21-25 have been rejected under 35 USC §103 (a) as being unpatentable over Mayo (WO98/47089 is the foreign counterpart to US Patent No. 6,188,965 issued February 13, 2001) in view of Applicants' disclosure of known prior art.

To establish a *prima facie* case of obviousness, three basic criteria must be met: 1) suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify or combine reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art reference must teach or suggest all the claim limitations. (See MPEP §2142).

With respect to the first criterion, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify or combine reference teachings. The Examiner acknowledges Mayo does not disclose the synthesis of the protein or the nucleotides that would encode the protein. One of ordinary skill would understand the cited "DNA shuffling" reference and other well-known mutagenesis techniques, teach away from the use of a rational computational design algorithm, as used in the instant application. Furthermore, there is no suggestion or motivation to modify or combine the teachings with Mayo. Therefore, the first prong of the analysis has not been met.

The second criterion, a reasonable expectation of success, has been demonstrated in several working examples have been included in the application as filed. See Specification at pages 60-67. Additional support for the expectation of success may be found in the following publications: Filikov et al., Protein Science, 11:1452-1461 (2002) (Exhibit B) and Luo et al., Protein Science 11:1218-1226, (2002) (Exhibit C). Copies of the afore-mentioned publications have been attached hereto for the Examiner's convenience.

Finally, the prior art reference must teach or suggest all the claim limitations. As discussed above, neither prior art reference teaches or suggests all the claim limitations of the present invention. As discussed above, Mayo does not disclose generating a library of protein variants. With respect to the prior art cited by the Examiner, e.g. "DNA shuffling," the reference does not disclose generating a probability distribution table of amino acid residues in a plurality of variant positions utilizing a force field, as required by the present invention. In light of the above-facts, neither of the cited prior art references teaches or suggests all the claim limitations and do not support the third criterion.

"A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert denied, 469 U.S. 851 (1984)."

Applicants respectfully submit, in light of the foregoing discussion, neither reference supports a finding that a *prima facie* case of obviousness has been established against the present invention.

The Applicants submit that in light of the above-amendment and argument, the claims are now in condition for allowance and an early notification of such is respectfully solicited.

Attached hereto is a marked-up version of the changes made to the claims by the "Amendment". The attached page is captioned **"Version with markings to show changes made."** Please direct any calls in connection with this application to the undersigned at (626) 737-8019.

Respectfully submitted,

Dated: April 2, 2003

By: _____

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VERSION TO SHOW CHANGES MADE

In the Specification:

Page 12, lines 22-25.

The source of the sequences can vary widely, and include taking sequences from one or more of the known databases, including, but not limited to, SCOP (Hubbard, et al., Nucleic Acids Res 27(1):254-256. (1999)); PFAM (Bateman, et al., Nucleic Acids Res 27(1):260-262. (1999)); VAST (Gibrat, et al., Curr Opin Struct Biol 6(3):377-385. (1996)); CATH (Orengo, et al., Structure 5(8):1093-1108. (1997)); PhD Predictor ~~[(http://www.embl-heidelberg.de/predictprotein/predictprotein.html)]~~ (Rost B, Sander C, Schneider R., PHD--an automatic mail server for protein secondary structure prediction. Comput Appl Biosci. 1994 Feb;10(1):53-60); Prosite (Hofmann, et al., Nucleic Acids Res 27(1):215-219. (1999)); PIR ~~[(http://www.mips.biochem.mpg.de/proj/protseqdb/)]~~ (Wu CH, Yeh LS, Huang H, Arminski L, Castro-Alvear J, Chen Y, Hu Z, Kourtesis P, Ledley RS, Suzek BE, Vinayaka CR, Zhang J, Barker WC, The Protein Information Resource, Nucleic Acids Res. 2003 Jan 1;31(1):345-7.); GenBank ~~[(http://www.ncbi.nlm.nih.gov/)]~~ (ncbi.nlm.nih.gov); PDB ~~[(www.resb.org)]~~ (H. M. Berman, T. Battistuz, T. N. Bhat, W. F. Bluhm, P. E. Bourne, K. Burkhardt, Z. Feng, G. L. Gilliland, L. Iype, S. Jain, P. Fagan, J. Marvin, D. Padilla, V. Ravichandran, B. Schneider, N. Thanki, H. Weissig, J. D. Westbrook and C. Zardecki, The Protein Data Bank, Acta Cryst. (2002). D58, 899-907); and BIND (Bader, et al., Nucleic Acids Res 29(1):242-245. (2001)).

Page 13, lines 21-28.

Similarly, structural alignment of structurally related proteins can be done to generate sequence alignments. There are a wide variety of such structural alignment programs known. See for example VAST from the NCBI ~~[(http://www.ncbi.nlm.nih.gov:80/Structure/VAST/vast.shtml)]~~ (Gibrat, et al., Curr Opin Struct Biol 6(3):377-385. (1996)); SSAP (Orengo and Taylor, Methods Enzymol 266(617-635 (1996)) SARF2 (Alexandrov, Protein Eng 9(9):727-732. (1996)) CE (Shindyalov and Bourne, Protein Eng 11(9):739-747. (1998)); (Orengo et al., Structure 5(8):1093-108 (1997); Dali (Holm et al., Nucleic Acid Res. 26(1):316-9 (1998), all of which are incorporated by reference). These structurally-generated sequence alignments can then be examined to determine the observed sequence variations.

Page 13, line 29 through page 14, line 5.

Primary libraries can be generated by predicting secondary structure from sequence, and then selecting sequences that are compatible with the predicted secondary structure. There are a number of secondary structure prediction methods, including, but not limited to, threading (Bryant and Altschul, Curr Opin Struct Biol 5(2):236-244. (1995)), Profile 3D (Bowie, et al., Methods Enzymol 266(598-

616 (1996); MONSSTER (Skolnick, et al., J Mol Biol 265(2):217-241. (1997); Rosetta (Simons, et al., Proteins 37(S3):171-176 (1999); PSI-BLAST (Altschul and Koonin, Trends Biochem Sci 23(11):444-447. (1998)); Impala (Schaffer, et al., Bioinformatics 15(12):1000-1011. (1999)); HMMER (McClure, et al., Proc Int Conf Intell Syst Mol Biol 4(155-164 (1996)); Clustal W ~~[(http://www.ebi.ac.uk/clustalw/)]~~ (Higgins D., Thompson J., Gibson T.Thompson J.D., Higgins D.G., Gibson T.J.(1994). CLUSTAL W: improving the sensitivity of progressive multiple sequence alignment through sequence weighting,position-specific gap penalties and weight matrix choice. Nucleic Acids Res. 22:4673-4680); BLAST (Altschul, et al., J Mol Biol 215(3):403-410. (1990)), helix-coil transition theory (Munoz and Serrano, Biopolymers 41:495, 1997), neural networks, local structure alignment and others (e.g., see in Selbig et al., Bioinformatics 15:1039, 1999).

Please replace the paragraph found on page 2, lines 4-6 with the following paragraph.

In particular, U.S.S.N.s 60/061,097, 60/043,464, 60/054,678~~[, 09/127,926]~~; PCT US98/07254; and U.S.S.N.: 09/127,926, now US Patent No. 6,269,312, issued July 31, 2001, describe a method termed "Protein Design Automation", or PDA™, that utilizes a number of scoring functions to evaluate sequence stability.

In the Claims:

12. (Amended) A method for generating a secondary library of scaffold protein [variants] sequences comprising:

a) receiving a library of primary sequences generated utilizing a force field calculation;

[a)] b) generating a probability distribution table of amino acid residues in a plurality of variant positions from said primary sequences; and

[b)] c) combining a plurality of said amino acid residues to generate a secondary library of secondary sequences; wherein at least one of said secondary [variants] sequences is different from said primary [variants] sequences.

13. (Amended) A method according to claim 12, wherein said force field calculation is [SCMF] Self-Consistent Mean Field (SCMF).

15. (Amended) A method according to claim 14, wherein a Protein Design Automation ~~(PDA™)~~ program is used to recombine said secondary library.

16. (Amended) A method for generating a secondary library of scaffold protein variants comprising:

a) receiving a library of primary sequences generated utilizing an alignment program;

[a)] b) generating a probability distribution table of amino acid residues in a plurality of variant positions from said primary sequences;

[b)] c) combining a plurality of said amino acid residues to generate a secondary library of secondary sequences, wherein at least one of said secondary [variants] sequences is different from said primary [variants] sequences; and

[c)] d) computationally ranking said secondary library.

18. (Amended) A method according to claim 17, wherein a Protein Design Automation program ~~(PDA™)~~ is used to recombine said secondary library.

24. (Amended) A method according to claim ~~23~~ 22 wherein said pooled oligonucleotides are added in amounts that correspond to the frequency of the mutation.

26. (New) A method for generating a secondary library of scaffold protein sequences comprising:
a) generating a probability distribution table of amino acid residues in a plurality of variant positions from a force field calculation; and
b) combining a plurality of said amino acid residues to generate a secondary library of secondary sequences; wherein at least one of said secondary sequences is different from said primary sequences.

27. (New) A method according to claim 26 further comprising synthesizing a plurality of said secondary sequences.

28. (New) A method according to claim 27 wherein said synthesizing is done by multiple PCR with pooled oligonucleotides.

29. (New) A method according to 28 wherein said pooled oligonucleotides are added in equimolar amounts.

30. (New) A method according to claim 28 wherein said pooled oligonucleotides are added in amounts that correspond to the frequency of the mutation.

APPENDIX OF PENDING CLAIMS

12. (Amended) A method for generating a secondary library of scaffold protein sequences comprising:

a) receiving a library of primary sequences generated utilizing a force field calculation;

b) generating a probability distribution table of amino acid residues in a plurality of variant positions from said primary sequences; and

c) combining a plurality of said amino acid residues to generate a secondary library of secondary sequences; wherein at least one of said secondary sequences is different from said primary sequences.

13. (Amended) A method according to claim 12, wherein said force field calculation is Self-Consistent Mean Field (SCMF).

14. A method according to claim 12, further comprising computationally recombining said secondary library to generate a tertiary library.

15. (Amended) A method according to claim 14, wherein a Protein Design Automation program is used to recombine said secondary library.

16. (Amended) A method for generating a secondary library of scaffold protein variants comprising:

a) receiving a library of primary sequences generated utilizing an alignment program;

b) generating a probability distribution table of amino acid residues in a plurality of variant positions from said primary sequences;

c) combining a plurality of said amino acid residues to generate a secondary library of secondary sequences, wherein at least one of said secondary sequences is different from said primary sequences; and

d) computationally ranking said secondary library.

17. A method according to claim 16, further comprising computationally recombining said secondary library to generate a tertiary library.

18. (Amended) A method according to claim 17, wherein a Protein Design Automation program is used to recombine said secondary library.

19. A method according to claim 16, wherein said alignment program is a sequence alignment program.

20. A method according to claim 16, wherein said alignment program is a structural alignment program.

21. A method according to claims 12 or 16 further comprising synthesizing a plurality of said secondary sequences.

22. A method according to claim 21 wherein said synthesizing is done by multiple PCR with pooled oligonucleotides.

23. A method according to 22 wherein said pooled oligonucleotides are added in equimolar amounts.

24. (Amended) A method according to claim 22 wherein said pooled oligonucleotides are added in amounts that correspond to the frequency of the mutation.

26. (New) A method for generating a secondary library of scaffold protein sequences comprising:
a) generating a probability distribution table of amino acid residues in a plurality of variant positions from a force field calculation; and
b) combining a plurality of said amino acid residues to generate a secondary library of secondary sequences; wherein at least one of said secondary sequences is different from said primary sequences.

27. (New) A method according to claim 26 further comprising synthesizing a plurality of said secondary sequences.

28. (New) A method according to claim 27 wherein said synthesizing is done by multiple PCR with pooled oligonucleotides.

29. (New) A method according to 28 wherein said pooled oligonucleotides are added in equimolar amounts.

30. (New) A method according to claim 28 wherein said pooled oligonucleotides are added in amounts that correspond to the frequency of the mutation.